a link has been established through the case study presented and other medical evidence such as a propensity for mental illness from pregnancy complications that may be used in diagnosing a predisposition to schizophrenia. The actual diagnosis of schizophrenia must be made through clinical diagnosis. However, the presence of anti-Cw antibodies can be used as a tool for diagnosis of a predisposition, so that early intervention may be established thus resulting in a better prognosis.

Mouro *et al.* simply describe the molecular basis of the Rh blood group antigens, particularly that sequence analysis has indicated that the expression of Cw antigens are associated with point mutation in the RHCE gene and further describe a polymerase chain reaction assay useful for diagnosis purposes for determination of the Cw status of fetuses for the proper management of pregnancies in highly Cw immunized mothers. Anti-Cw was used in hemagglutination inhibition experiments. Curtin *et al.* and Bowman *et al.* both describe hemolytic disease due to anti-cw antibody. These references do not teach or suggest Applicant's discovery of a link between the presence of the anti-Cw antibody and a predisposition to psychosis but are evidentiary support of some of the adverse effects of a histocompatibility. The presence of the anti-Cw antibody in a progeny with Cw antigen is indicative of a histocompatibility, of which hemolytic disease is an example. These disorders are not unrelated, as the Examiner contends. A profound relationship exists between histocompatibility and hemolytic disease.

The result of a histocompatibility of the Cw antigen, can be a risk factor in schizophrenia. Additionally, the art provides other links. For example, a link between HLA histocompatibility and psychosis, in particular schizophrenia, has been established (Wright, P. *et al.*, "Schizophrenia and HLA: a review," *Schizophrenia Research*, 47(1):1-12, Abstract, Exhibit A)

The Examiner also argued the insufficiency of the case study. Applicant respectfully disagrees. The case study, in combination with the state of the art, sufficiently links the Cw antigen antibody with evidence to be used in aiding the diagnosis of one with psychosis, in particular, schizophrenia. The state of the art has established the link of HLA region to schizophrenia and psychosis through linkage studies on chromosome 6. The Hollister *et al.* (*Arch. Gen. Psychiatry*, 53(1): 19-24 (1996)) study concluded that Rh incompatibility contributes to schizophrenia. The locus of Cw is found on chromosome 6 in the HLA region. Lindholm *et*

al. report of a schizophrenia-susceptibility locus at 6q25 in one of the world's largest reported pedigrees (a 12 generation, 3,400 member family) (*Am. J. Hum. Genet.*, 69(1):96-105 (2001), Exhibit B). Although, the particular genes have not yet been identified, there is growing evidence that the areas of concern linking the same area that encodes the blood group antigens, *i.e.,* the same area that encodes the blood antigen, Cw. Also, these studies may indicate that there are small effector genes that relate to a subset of the schizophrenic population. For example, Bassett and Chow (*Biol. Psychiatry*, 46:882-891 (1999), Exhibit C) disclose that 22q11 deletion syndrome is a genetic subtype of schizophrenia. Lahdelma *et al.* disclose an association between HLA-A1 allele and schizophrenia gene(s) in patients refractory to conventional neuroleptics but responsive to clozapine medication (*Tissue Antigens*, 51:200-203 (1998), Exhibit D).

Applicant does not argue the schizophrenia is a genetically complex disorder and both genetic and environmental factors can contribute. Applicant has provided evidence to be used in **aiding** in a diagnosis by finding a predisposition to psychosis, particularly schizophrenia. Applicant found that the presence of the anti-Cw antibody can be indicative of a predisposition to psychosis. Applicant is not claiming that the presence of the anti-Cw antibody unequivocally is indicative of psychosis. However, detection of Cw antibody when used in combination with diagnostic methods can be used to proactively determine if a person is predisposed. Applicant has determined that the presence of the anti-Cw antibody is a such a risk factor which can be screened for in a schizophrenic assessement.

Environmental factors also contribute to schizophrenia. For example, Basset and Chow in *Biological Psychiatry*, 46(7):882-891 (1999), discuss certain risk factors and propose clinical criteria to aid in identifying patients with schizophrenia who have a genetically identifiably subtype of schizophrenia. Applicant's discovery of another risk factor (*i.e.,* presence of anti-Cw antibody) may contribute to better or early diagnosis.

The Examiner further stated, that "since Cw is relatively rare and no previous correlation has been demonstrated between the measurement of Cw antibodies and psychosis, a method attempting to link the two inherently encompasses a great amount of uncertainty, which the current state of the art is unable to remedy." Applicant respectfully disagrees with the Examiner's conclusion The art is filled with relevant and related studies to help show that the link between the presence of Cw antibodies and psychosis is not uncertain.

The incidence of Cw antigen is rare and coincidentally the same as schizophrenia, approximately 1% of the population is affected. Interestingly, Finland has both an increased incidence of Schizophrenia and Cw antigen. Also, certain ethnic populations have been implicated as being predisposed to a higher incidence of schizophrenia. Chowdari *et al.* describe immune related genetic polymorphisms, particularly in the HLA region, and schizophrenia among the Chinese (*Human Immunology*, 62:714-724 (2001), Exhibit E). The state of the art is filled with relevant and related studies, such as HLA linkage, histocompatibility, pregnancy complications and the exhibits presented herewith, that help to show this link is not uncertain.

In view of the above remarks and comments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection of Claims 1-13 under 35 U.S.C. §112, Second Paragraph

Claims 1-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Applicant has amended Claim 1 to indicated that the presence of the anti-Cw antibody is indicative of a histocompatibility between the mother and the progeny. Amended Claim 1 clearly indicates that the method aids in diagnosis and further that the presence of the anti-Cw antibody indicates a histocompatibility that may predispose one to psychosis. Antecedent basis issues have been corrected.

Claim 5 is amended to recite "a blood type which is the same".

Claim 6 is amended the claim to recite "a" presence.

Claims 7-9 have been amended to properly depend from Claim 6.

Claim 10 has been amended to clearly indicate that the sample contains Cw antibodies.

Claim 11 has been amended to correct antecedent basis issues.

In view of the above amendments, the amended claims are clear and definite. As such, Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested. Should the Examiner believe that prosecution of the application may be expedited by telephone conference with the Applicant's Agent, please call the undersigned at the number given below.

Respectfully submitted,
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Dated: February 11, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method for aiding in the diagnosis of [diagnosing] a predisposition to psychosis in a progeny who possesses Cw blood antigen, comprising:

(a) obtaining a biological sample from the progeny's mother [of the progeny]; and

(b) determining [the] presence of anti Cw antibody in the biological sample, wherein the presence of an anti Cw antibody in the biological sample is indicative of a histocompatibility and a predisposition of the progeny to psychosis.

5. (Amended) A method as in claim 1 wherein the mother and progeny have [the same] a blood type which is the same.

6. (Amended) A method of screening for predisposition to psychosis, comprising:

(a) obtaining a sample from a maternal donor; and

(b) determining [the] presence of an anti-Cw antibody in the sample, wherein the presence of an anti-Cw antibody is indicative of a predisposition to schizophrenia if donor's progeny possess Cw antigen.

7. (Amended) A method as in Claim [8] 6 wherein the progeny has a family history of psychosis.

8. (Amended) A method as in Claim [8] 6 wherein the donor is pregnant.

10. (Twice Amended) A kit for use in diagnosis of psychosis, comprising a sample [of] containing anti-Cw, a detector that binds to anti-Cw antibody, and instructions for using the antibody and detector to diagnose a predisposition to psychosis.

11. (Amended) A method for diagnosing or aiding in the diagnosis of a predisposition to a psychotic disorder, comprising determining [the] presence of anti-Cw antibody in a sample from an individual with Cw antigen, wherein the presence of anti-Cw antibody indicates a positive diagnosis.

12. (Amended) A kit for use in diagnosis of psychosis, comprising a sample [of] containing anti-Cw antibody, a detector that binds to anti-Cw antibody; and instructions for utilization of the kit according to the method of Claim 1.